priority" generally is used to refer to rights under 35 USC §119. The term "right of priority" generally is not used in connection with rights under 35 USC §120.

It is clear that "a method of treating chronic rheumatoid arthritis" is entitled to the benefit under 35 USC §120 of Serial No. 08/268,520. That application discloses the use of IL-6 antibodies as the active ingredient in a composition to treat "chronic arthritic rheumatism" (page 7, lines 18-31). Accordingly, claims to treating chronic rheumatoid arthritis in the present application are entitled to benefit under 35 USC §120 of the June 30, 1994, filing date of Serial No. 08/268,520 (now 08/971,997).

Under 35 USC §119, claims in the present application that are drawn to methods of treating chronic rheumatoid arthritis are entitled to an even earlier date. Applicants claim the benefit under 35 USC §119 of the following three Japanese applications:

JP 6-244035	filed October 7, 1994
JP 5-210570	filed August 25, 1993
JP 5-180303	filed July 21, 1993

A sworn translation of JP 5-180303 was made of record on January 22, 1998, and sworn translations of the other two Japanese applications are forwarded herewith.

JP 6-244035 discloses "a synovial cell growth inhibitor" (page 2, lines 1-13; page 6, line 15) and "a pharmaceutical composition for inhibiting abnormal growth of synovial cells" (page 5, lines 20-22). Effects on synovial cell growth are documented on page 23 of the translation, *inter alia*. Therefore, claims to "a method

of inhibiting synovial cell growth" or claims that recite "suppresses abnormal growth of synovial cells" are entitled under 35 USC §119 to a date of October 7, 1994. This date is earlier than the 1995 publication date of Mihara *et al.* and thus Mihara is effectively antedated as to claims that recite methods of inhibiting synovial cell growth (claims 19-23) and claims that recite suppression of abnormal growth of synovial cells (claim 25).

JP 5-180303 discloses the use of an anti-sIL-6R antibody for treating various diseases, including "chronic rheumatoid arthritis" (page 14, lines 8-17 of translation). Therefore, claims to treating chronic rheumatoid arthritis in the present application are entitled to benefit under 35 USC §119 of the July 21, 1993, filing date of JP 5-180303, a date which is earlier than the June 30, 1994, date to which they are entitled under 35 USC §120 based on Serial No. 08/268,520. This date is earlier than the August 1994 publication date of Sipe *et al.*

Claims 24 and 26-29, directed to a method of treating chronic rheumatoid arthritis are rejected under §103(a) based on U.S. 5,591,827 in view of Sipe *et al.* and Hirata *et al.* The '827 patent teaches the use of IL-6 receptor antagonists in treating IL-6 related diseases. The antagonists are mutated IL-6 polypeptides (see claim 1). As admitted by the examiner, antibodies to IL-6 receptor are not suggested. Sipe is cited as teaching that the destruction of joints caused by rheumatoid arthritis is due in part to the action of destructive cytokines such as IL-1 and IL-6, and that potential agents for modulation of cytokine production and/or action

include anti-cytokine and anti-cytokine receptor antibodies. Hirata is relied upon as teaching a monoclonal antibody, PM1, which binds to an epitope on the IL-6 receptor and blocks the binding of IL-6 to the receptor. The examiner urges that "it would have been obvious...to substitute the PM1 antibody of Hirata for the monoclonal antibodies of the '012 patent [sic: '827 patent?] for administration in a manner consistent with the '827 patent...one would have been motivated to combine the references with a reasonable expectation of success by the teaching of Sipe *et al.* that monoclonal antibodies to cytokine receptors are effective agents for blocking the destructive action of cytokines in RA."

As noted above, claims to a method of treating chronic rheumatoid arthritis, such as claims 24 and 26-29, are entitled to a date of August 1994, and Sipe *et al.* is not effective as a reference against these claims. Sipe *et al.* provides the link between the '827 patent and Hirata. Without Sipe, the alleged *prima facie* case of obviousness must fail, since there is then no teaching that destructive cytokines are implicated in destruction of joints caused by rheumatoid arthritis, and that anti-cytokine receptor antibodies are potential agents for modulation of cytokine action or production. Accordingly, reconsideration and withdrawal of the rejection of claims 24 and 26-29 is requested.

Even assuming, *arguendo*, that Sipe could be shown to be effective as a reference against the present claims 24 and 26-29, its disclosure fails to render obvious the subject matter of those claims. The examiner urges that "the Sipe *et al.* reference teaches that the destruction of

joints caused by rheumatoid arthritis (RA) is due in part to the action of destructive cytokines such as IL-1 and IL-6 and can be modulated at multiple points associated with either cytokine action or production." Sipe *et al.* further teaches that potential agents for this modulation include anti-cytokine and anti-cytokine receptor antibodies."

These teachings in Sipe *et al.* do not lead to the conclusion that anti-IL-6 receptor antibody can be used to treat RA. In the first instance, a ***correlation*** between IL-6 and RA does not mean that IL-6 is ***cause*** of RA. That is, production of IL-6 may be a ***result*** of RA, and not a ***cause***. If the production of IL-6 is a ***result*** of RA, then inhibition of IL-6 will not be effective to treat the cause of the disease.

Furthermore, as noted by the examiner, "Sipe *et al.* clearly teaches in the Abstract '[a] ***complex cytokine network perpetuates joint conditions*** *by direct regulation of metalloproteases,* ***by indirect recruitment of cells that secrete degradative enzymes, and by inhibition of reparative processes*** (Action at page 4, emphasis in original). The very complexity of the cytokine network noted by Sipe and cited by the examiner militates against a conclusion of obviousness. The cytokine network is formed of a large number of individual cytokines. It is well known in the art that interaction of cytokines in the network is very complicated, and different cytokines exhibit various actions, many of which overlap. For example, in many cases two cytokines will have a common action, such that blocking of one of the two cytokines will have little or no overall effect since the other

cytokine exhibits the same action and compensates for the blocked cytokine. The blocking of one cytokine in the network does not necessarily result in the blockage of the cytokine network.

Finally, even the question of whether IL-6 has a favorable or detrimental action on RA is a matter of debate. Sipe *et al.* state that "IL-6 has no direct effects on the synthesis of proteases, prostaglandins or matrix protein, but stimulates synthesis of TIMP" (page 247, first sentence), and "in this manner, IL-6 production would counteract the degradative potential of IL-1" (bottom of the left-hand column of page 248). Thus, IL-6 may exert an overall positive effect in RA.

Like Sipe, other art teaches that interaction of cytokines in the network is very complicated, so that the role played by a given cytokine in a disease state cannot be certain. For example, Strand reveals that "the complexity of the immune system, exemplified by the pleiotropic effects of many cytokines and the redundancy of regulatory networks controlling immune responses, suggests that a single therapeutic interventions will offer transient or less than clinically meaningful results. *J. Rheumatol. Suppl.* **44**: 91-96 (1996), page 91 (abstract) - copy appended. In Barthel and Burmester there is an elaboration of this theme. In particular, they note that there is no evidence of which cytokines, if any, are the "activating triggers" in RA, and which cytokines are "downstream cytokines" or a "self-perpetuating network." *Ann. Rheum. Dis.* **54**:948-950 (1995), paragraph bridging page 948 and 949, and the following two paragraphs on page 949 - copy appended.

Durum reports that "all the aforementioned complex *in vitro* interactions of cytokines make it virtually impossible to predict the *in vivo* activities of a given cytokine. This is amply illustrated by the unexpectedly broad spectrum of *in vivo* activities of cytokines such as IL-1, TNF, TGF-β and IL-6. The actual physiological role of most of the cytokines remains to be established. In fact, we have to relearn the trite but true import of '*in vivo veritas*.'" Fundamental Immunology, (3rd ed.), 1993, Chapter 21, page 826, first column, second full paragraph - copy appended. Finally, Henderson reveals that "our expectations that blocking single cytokines (by complex agents such as cloned chimaerised antibodies or soluble receptor-antibody complexes) can inhibit tissue pathology should remain at a sensible low level. Only time will tell if it is possible to inhibit complex cytokine induced pathology in man by removing single cytokines." *Ann. Rheum. Dis.* **54**:519-523 (1995), page 522, final paragraph - copy appended.

The complexity of the cytokine network is well documented, and the role played by IL-6 in RA was unknown. Accordingly, to allege a therapeutic affect for anti-IL-6 receptor antibodies in the treatment of RA is speculative, at best. In the absence of *in vivo* animal model data, such as that provided in applicants' specification, any case of obviousness based on disclosure such as that found in Sipe *et al.* is unsupported.

Claims 19-29 stand rejected under §103(a) based on U.S. 5,591,827 in view of Sipe *et al.*, Hirata *et al.*, Sack *et al.* and Mihara *et al.* Claims 24 and 26-29 are directed to a method of treating chronic rheumatoid arthritis and

are entitled to the benefit under 35 USC §119 of the July 21, 1993, date of JP 5-180303. Claim 25 also is directed to a method of treating chronic rheumatoid arthritis, but recites that the antibody is one that "suppresses abnormal growth of synovial cells." Claim 25 is entitled under 35 USC §119 to at least a date of October 7, 1994, since JP 6-244035 discloses that IL-6 receptor antibodies inhibit abnormal growth of synovial cells (page 5, lines 20-22). Claims 19-23 also are entitled to a date of October 7, 1994, since they are directed to a method inhibiting synovial cell growth.

Mihara is not effective as a reference against any of claims 19-29, since all of claims 19-29 are entitled to the benefit of a date that is earlier than the 1995 publication date of Mihara. Mihara is cited as teaching that the presence of excess IL-6 and soluble IL-6 receptor in the synovial fluid stimulates the proliferation of synovial cells, and that treating IL-6 stimulated synovial cells with anti-IL-6 or anti-IL-6 receptor antibodies effectively reduces the proliferation of synovial cells. Absent this teaching it would not have been obvious to combine the references in the manner urged.

More particularly, the only other reference which relates to the synovium is Sack *et al.* The examiner argues that Sack teaches that IL-6 is "closely associated with synovitis" and "positively correlated with histological characteristics thereof." However, a teaching of a positive correlation between histological characteristics of synovitis and the level of IL-6 in synovial fluid falls far short of Mihara's teaching that the presence of excess IL-6 and soluble IL-6 receptor in

the synovial fluid stimulates the proliferation of synovial cells, and that treating IL-6 stimulated synovial cells with anti-IL-6 or anti-IL-6 receptor antibodies effectively reduces the proliferation of synovial cells. Indeed, Sack note that "it is still a matter of debate whether IL-6 could act as a protective cytokine in inflammation by inducing acute phase reactants, *i.e.*, metalloproteinase inhibitors, which in turn could counteract joint destruction" (page 50, first full paragraph in right-hand column). Thus, a "positive correlation" does not establish that a causal relationship exists between high levels of IL-6 in the synovial fluid and histological characteristics of chronic synovitis. Thus, the rejection of claims 19-29 must fail absent Mihara's teaching.

As noted above, claims 24 and 26-29, to a method of treating chronic rheumatoid arthritis, are entitled to a date of August 1994, and neither Mihara *et al.* nor Sipe *et al.* is effective as a reference against these claims. Without Sipe, the alleged *prima facie* case of obviousness contains a further deficiency, since there is then no teaching that destructive cytokines are implicated in destruction of joints caused by rheumatoid arthritis, and that anti-cytokine receptor antibodies are potential agents for modulation of cytokine action or production. The only document other than Sipe and Mihara that relates to chronic rheumatoid arthritis is Sack. Sack's disclosure, relating a "positive correlation" between high levels of IL-6 in the synovial fluid and histological characteristics of chronic synovitis in RA, does not establish that a causal relationship exists between IL-6 and rheumatoid arthritis, as detailed above.

In view of the amendments to the claims and the foregoing remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, Examiner Vandervegt is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

September 10, 1998
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The Commissioner is hereby authorized to charge any fee required by the filing of this response to Deposit Account No. 19-0741.